REMARKS

This responds to the Office Action mailed on January 29, 2009.

Claims 58-68 have been added. Thus, claims 35-68 are now pending in the application. However, the Examiner has withdrawn claims 51-56 from examination as a result of the restriction requirement. Accordingly, claims 35-50 and 57-68 are now under examination.

New claims 58 and 59 are directed to products and compositions wherein the 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof, consists of greater than 90% 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof. Support for this subject matter is present throughout the specification, for example, at page 5, lines 5-9.

Support for new dependent claims 60-68 is also found throughout the specification and claims as originally filed. For example, the subject matter of new claims 60-68 is supported by current claims 39-48, respectively. Further support for new claim 60, drawn to compositions with less than 5% 3,11b-*trans*-dihydrotetrabenazine, is found at page 5, line 15-19. Support for new claim 61, which defines the 3,11b-*cis*-dihydrotetrabenazine or the salt thereof as a (+)-isomer, is present in original claims 3 and 6. Support for new claims 62-65, which define the 3,11b-*cis*-dihydrotetrabenazine as having formula (Ia) - (Id), respectively, can be found throughout the specification as filed, for example, in original claims 7-10 and at page 6, line 16 to page 7, line 8. Support for the subject matter of claim 66, which defines the 3,11b-*cis*-dihydrotetrabenazine as a free base, is present, for example, in original claim 21, and at page 9, lines 6-9. Support for the subject matter of claims 67 and 68, which recite that the 3,11b-*cis*-dihydrotetrabenazine is in the form of an acid addition salt and a methane sulponate salt, respectively, is present, for example, in original claims 22-23.

Claims 39-48 and 50, as well as withdrawn claims 52-54, have been amended.

Claim 39 has been amended to recite "with" rather than "and containing" less than 5% of 3,11b-*trans*-dihydrotetrabenazine.

Claims 40-48, 50 and 52 have been amended to recite "The" rather than "An" or "A," to indicate that there is antecedent basis for the product or composition of these dependent claims in the referenced independent claim.

The terms "the" and "where required" have been deleted from withdrawn claims 53 and 54.

Applicant submits that no new matter has been added to the application.

Restriction Requirement

Applicants acknowledge the Examiner's comments on the Restriction Requirement and reserve the right to petition for rejoinder and/or to file a continuation or divisional application drawn to the unelected claims.

§103 Rejection of the Claims

The Examiner has made three rejections of the claims under section 103, which are separately discussed below.

Claim 35 and 42

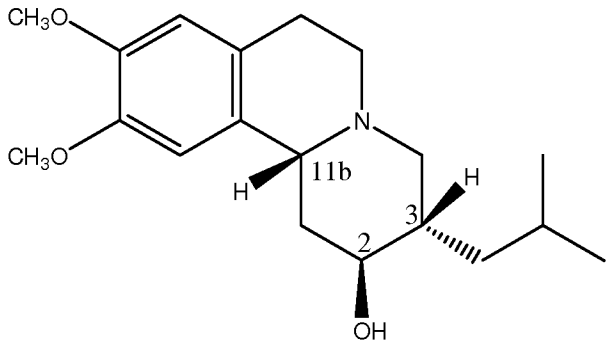
Claims 35 and 42 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kilbourn et al. (Eur J Pharmacol, 278:249-252, 1995; hereinafter "Kilbourn") in view of Williams et al. (Foye's Principles of Medicinal Chemistry, Page 50, 2002; hereinafter "Williams").

According to the Examiner, dihydrotetrabenazine is known. The Examiner asserts that Kilbourn discloses that dihydrotetrabenazine contains three asymmetric carbon centers (C-2, C-3 and C-11 b), and that two isomers at the C-2 carbon can be easily resolved by column chromatography to form α- and β- dihydrotetrabenazine. According to the Examiner, Kilbourn teaches that α-dihydrotetrabenazine has four possible isomers, citing page 249, column 2 of the Kilbourn reference. However, the

Examiner expressly acknowledges that Kilbourn does not explicitly disclose Applicant's elected species (Office Action, page 5), which is shown in Applicant's claim 42.

Claim 35 is drawn to 3,11b-*cis*-dihydrotetrabenazine or a salt thereof.

Claim 42 recites that the 3,11b-*cis*-dihydrotetrabenazine or a salt thereof is in the form of a 2*S*,3*S*,11b*R* isomer having the formula (Ia):



(Ia).

Applicant submits that this rejection under 35 U.S.C. 103(a) fails for the following reasons:

1) This is not a case about resolution of a racemate. The invention is based on the development and synthesis of new compounds that, to Applicants knowledge, did not previously exist. If trace levels of Applicants' compounds did exist in some undiscovered manner (of which Applicants are unaware), Applicants submit that the compounds could only have been present in exceedingly small amounts.

2) The prior art provides no motivation for one of skill in the art to even consider the compounds of the invention. Instead, the prior art contains teachings that would guide the skilled person away from the compounds of the invention.

3) T*he trans*-dihydrotetrabenazines were first published 46 years before the priority date of the present invention. The fact that the prior art was silent about the *cis*-dihydrotetrabenazines for such a prolonged period is factual evidence that the compounds of the present application were not obvious.

4) The prior art teaches no methods by which the compounds of the claims can be obtained. Faced with this difficulty, the skilled person would have been deterred from making the compounds of the invention. Rather than try to make the *cis*-dihydrotetrabenazines, the skilled person would have been more likely to investigate analogs and derivatives of the *trans*-dihydrotetrabenazines that could be made by well established methods.

5) The compounds of the invention exhibit unexpected benefits that are not predictable from the prior art disclosures relating to the known *trans*-dihydrotetrabenazines. Evidence of the surprising properties of the compounds of the invention is set forth in the patent specification. The surprising properties of the compounds strongly support the patentability of the claims.

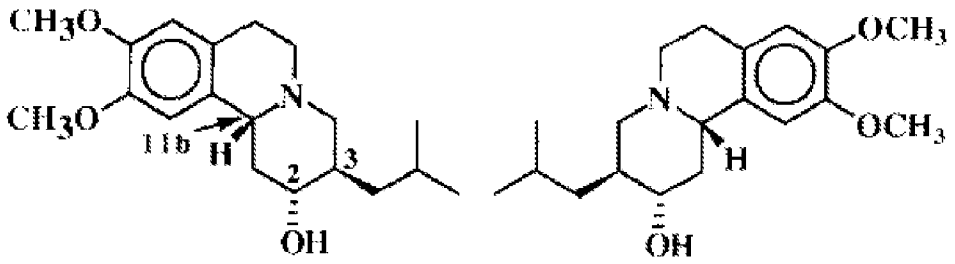
Invention is Not About Resolution of a Racemate

The *cis* isomers of dihydrotetrabenazine were not available in the prior art in any form (even in impure form) in any appreciable amount, as far as Applicants are aware. Kilbourn discloses that the only isomers of dihydrotetrabenazine are *trans* isomers. Williams discloses nothing whatsoever about dihydrotetrabenazine, tetrabenazine or any related benzoisoquinolines. Accordingly, Applicants submit that no one of skill in the art could simply purify *cis*-dihydrotetrabenazine isomers from existing preparations of *trans*-dihydrotetrabenazine or tetrabenazine.

Kilbourn informs one of skill in the art that only the two isomers at carbon-2 (C-2) can readily be isolated and calls these two C-2 isomers the α- and β-isomers of dihydrotetrabenazine.[1] Kilbourn further instructs the skilled artisan that it is surprising that the isomers at C-3 and C-11b have never been assessed but then reports that *extensive* NMR studies of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines have *established* the *fixed* relative configurations at the C-3 and C-11b positions.[2]

The *fixed* configurations of the prior art α-dihydrotetrabenazine enantiomers are shown in Kilbourn's Fig. 1, which is reproduced below for easy reference:

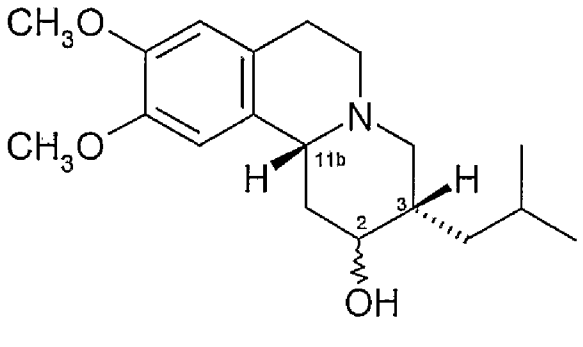
[1] Kilbourn, page 249, right column.
[2] *Id.*



Kilbourn Fig. 1

As shown, these compounds are both *trans* isomers with respect to the hydrogen atoms in the C-3 and C-11b positions. Thus, Kilbourn teaches those of skill in the art that the existing preparations of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines *all* have the hydrogens at the C-3 and C-11b positions in a *fixed* *trans* configuration.

Unlike the *trans* isomers disclosed by Kilbourn, Applicant's claim 35 is drawn to the *cis* isomer[3] with the structure shown below, which is racemic with respect to the C-2 position.



(I)

Thus, not only does the combination of Kilbourn and Williams fail to disclose Applicants isomers but, in consulting Kilbourn and Williams, one of skill would understand that all the known isomers of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines are *trans* isomers. After all, Kilbourn expressly states that

[3] As explained in Applicant's specification, use of the terminology "3,11b-*cis*" means that the hydrogen atoms at the 3- and 11b- positions of the dihydrotetrabenazine are in the cis orientation. See Applicant's specification page 6, lines 7-9.

extensive NMR studies were performed on the available preparations not only of α-dihydrotetrabenazine, but also of tetrabenazine and related benzoisoquinolines, and these studies *established* the *fixed* relative configurations at the C-3 and C-11b positions.[4] These statements alert one of skill in the art that alternative *cis* isomers at the C-3 and C-11b positions cannot be made in the same way that the *trans* isomers are made, and/or the cis isomers are so unstable that they essentially do not exist. Thus, Kilbourn discourages the skilled artisan from attempting to make the *cis* isomers of Applicant's claims.[5]

Williams fails to cure the deficiencies of Kilbourn. Instead, Williams provides only general information about isomers, and discloses nothing whatsoever about any isomers of tetrabenazine or dihydrotetrabenazine.

Hence, this is not a case about purification of one isomer from a mixture of isomers. Instead, only the *trans* isomers were available prior to Applicant's invention and no one knew how to make the *cis* isomers until Applicant's invented the appropriate procedures. Proof that no one had previously made the *cis* isomers, or knew how to make the *cis* isomers, is provided by the Kilbourn disclosure, which instructs one of skill in the art that all tetrabenazine and dihydrotetrabenazine compounds have a *fixed trans* configuration.

Silence in the Art for 46 Years about Applicant's Cis Isomers

The 3,11b *trans*-dihydrotetrabenazines were first disclosed in the patent and scientific literature in 1958,[6] forty-six years before the priority date of the present invention. However, during this forty-six year period the prior art has been entirely silent

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[4] Kilbourn, page 249, right column.

[5] The Examiner has admitted in the Office Action at page 4 that Kilbourn is limited to isolation and characterization of just two isomers dihydrotetrabenazine, which he calls the (+) and (-) α-isomers.

[6] See, U.S. Patent 2,843,591 published July 15, 1958; and Brossi *et al.*, *Helv. Chim. Acta* 41(16): 119 (1958). which both disclose only tetrabenazine and derivatives thereof (but not Applicant's *cis* isomers). For example, Brossi teaches that "Most of these ketones are substituted in the 3-position by a hydrogen radical which is in the *cis* position relative to the hydrogen on the carbon 11b and is not epimerised by acids and bases." See Brossi Translation at page 1. Thus, Brossi discloses compounds where the hydrocarbon in the 3-position is *cis* to the hydrogen in the 11b-position, meaning that the two hydrogens in the 3 and 11b positions are in *trans*. In contrast, Applicant's compounds have the two hydrogens at positions 3 and 11b in *cis* to one another while the hydrocarbon in the 3-position is *trans* to the hydrogen in the 11b-position.

as to the existence of the 3,11b *cis*-isomers and methods for making the 3,11b *cis*-isomers. This is evident from the Examiner's inability to find art more relevant than the Kilbourn disclosure, which only discloses 3,11b *trans*-isomers, and from Kilbourn's teachings that *extensive* NMR studies of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines have *established* the *fixed* relative configurations at the C-3 and C-11b positions.[7]

Nor did Kilbourn provide any person of skill in the art with the motivation to seek the *cis* isomers when it was published in 1995, or in 1996, or in any of the years between 1995 and the filing date of Applicants' application. Even Williams' general teachings on isomers failed to contribute sufficient information or motivation to encourage one of skill in the art to make the *cis* isomers. Despite Williams' teachings that different isomers can have different biological properties, no one was either motivated enough or capable enough to actually develop synthetic methods for making the 3,11b *cis*-isomers until Applicants did so.

No methods Existed for Making *cis*-3,11b Dihydrotetrabenazine Compounds

One reason that isolation and characterization of the *cis* isomers by others was so slow is that no one knew how to make them. The prior art discloses reactions (e.g. reduction) of tetrabenazine and derivatives/analogs thereof but, so far as the Applicants are aware from their own searches and the searches carried out by the EPO and UK Patent Offices, all prior art disclosures of compounds in which a substituent is present at the 3-position are of compounds that have the 3,11b-*trans*-stereochemistry. No one apparently knew that Applicant's *cis* isomers could actually exist and no one knew how to make them.

3,11b-*trans*-dihydrotetrabenazine can be made by straightforward reduction of 3,11b-*trans*-tetrabenazine. However, the 3,11b *cis*-dihydrotetrabenazines of the invention cannot be made in this way because this *cis* isomer does not form in detectable amounts when 3,11b-*trans*-tetrabenazine is reduced.

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[7] Kilbourn, page 149, right column.

Therefore, even if the skilled person had contemplated 3,11b *cis*-dihydrotetrabenazine isomers,[8] that skilled person would have been faced with the obstacle of devising a synthetic route that would yield appreciable amounts of the *cis* compounds. In view of this difficulty, it would have been more logical for the skilled person to continue to make further compounds having the 3,11b-*trans*-stereochemistry using easily available starting materials and standard methods, rather than to develop a new synthetic route for compounds that he or she would have had no reason to believe could be made or would have improved properties.

Thus, while Kilbourn was able to quickly resolve the *trans* (+) and (-) isomers using a one step HPLC process, no such simple procedure could be used for making the *cis* isomers of Applicant's claims. For example, Kilbourn provides just 1-2 paragraphs[9] describing how to make the *trans* (+) and (-) isomers disclosed therein. In contrast, Applicants provide at least 24 pages of teachings on how to synthesize the *cis* isomers recited in the claims.[10] Rather than the simple isomer purification procedure disclosed by Kilbourn, Applicants had to develop new synthetic (not just purification) procedures that are significantly more complicated and are in no way obvious from the Kilbourn and/or Williams disclosures.

Applicant's *Cis* Isomers Exhibit Unexpected Properties

Applicant's *cis* isomers have several unexpected properties that represent a significant advance over the prior art tetrabenazine compound and its *trans*-dihydrotetrabenazine isomers.

For example, tetrabenazine is known to have side effects such as depression, parkinsonism, drowsiness, nervousness or anxiety, insomnia and, in rare cases neuroleptic malignant syndrome.[11] *Trans*-dihydrotetrabenazine is the active metabolite

[8] The skilled artisan would not contemplate making the *cis* isomers for reasons described herein.
[9] Kilbourn at page 250.
[10] See, Applicants' specification at pages 10-18, 23-33, and 36-39.
[11] See, Applicant's specification page 1, lines 17 to 22; see also page 18, line 11 to page 19, line 19.

responsible for the therapeutic properties of the commercial form of tetrabenazine.[12] Therefore, as the active metabolite of tetrabenazine, *trans*-dihydrotetrabenazine is likely responsible for these side effects. This conclusion is supported by the disclosures of earlier documents relating to dihydrotetrabenazines. For example, U.S. Patent 2,843,591[13] discloses that the dihydrotetrabenazines have sedative properties.[14] Sedative properties for dihydrotetrabenazines are also mentioned an article by Brossi *et al.*[15]

In contrast, three of the four compounds of the present invention have been tested in sedation studies and have been found to be essentially non-sedating.[16] Thus, the tests described in Example 11[17] of the present application describe sedation studies comparing two compounds of the present invention (isomers B and C) with tetrabenazine.

> The results demonstrate that tetrabenazine produces a dose-dependent sedative effect 45 minutes and 3 hours after administration whereas Isomer B and Isomer C show no sedative effects at any time ...[18]

Because the *trans*-dihydrotetrabenazine isomers are the active metabolites of tetrabenazine, Applicant's B and C *cis* isomers exhibit such improved non-sedating effects relative to the prior art *trans*-dihydrotetrabenazine isomers.

The non-sedating properties of the compounds of the invention are entirely unexpected in view of the known properties of tetrabenazine and its *trans*-dihydrotetrabenazine metabolites. Such properties are a substantial advance over tetrabenazine and its *trans*-dihydrotetrabenazine metabolites.

Moreover, four compounds of Applicant's claims are essentially inactive against the Dopamine Transporter (DAT) transporter, indicating that Applicant's cis isomers do not have the dopaminergic side effects exhibited by tetrabenazine.

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[12] See, Applicant's specification at page 2, lines 16 to page 3, line 2.
[13] Provided in the Information Disclosure Statement submitted herewith.
[14] See, U.S. Patent 2,843,591 at col. 2, line 69.
[15] *Helv. Chim. Acta* at 119, 128 (1958); *see* Translation of Brossi article at page 5.
[16] See, Example 11 of Applicant's specification; and EP Patent Application 05708289.3, Response to Office Action (Sep. 17, 2007)(submitted herewith in an Information Disclosure Statement). Note that EP Patent Application 05708289.3 is the corresponding European patent application.
[17] See Applicant's specification at pages 56 to 61.
[18] *Id.* at page 61.

> Surprisingly, isomers C and B also show a remarkable separation of VAMT2 and dopamine receptor activity in that although they are highly active in binding VMAT2, both compounds exhibit only weak or non-existent dopamine receptor binding activity and lack Dopamine Transporter (DAT) binding activity. **In fact, none of the isomers exhibit significant DAT binding activity.** This suggests that the compounds may lack the dopaminergic side effects produced by tetrabenazine.[19]

The lack of DAT binding activity of the present compounds is demonstrated by the data in Table 6 of Applicant's specification.[20] As can be seen, each of the four compounds of the invention is essentially inactive against the DAT transporter. Such results could not have been predicted on the basis of the known properties of tetrabenazine and its *trans*-dihydrotetrabenazine active metabolites.

Neither Kilbourn nor Williams disclose any such advantageous properties for dihydrotetrabenazine isomers, or any related compounds. Nowhere does Kilbourn or Williams teach that any dihydrotetrabenazine isomers can avoid the sedative side effects associated with tetrabenazine. Nowhere does Kilbourn or Williams teach or suggest that any dihydrotetrabenazine isomers can exhibit negligible binding to dopamine receptors. Nowhere does Kilbourn or Williams teach or suggest that any dihydrotetrabenazine isomers can avoid the dopaminergic side effects encountered with tetrabenazine. Nowhere does Kilbourn or Williams teach that any dihydrotetrabenazine isomers have antidepressant activity. Accordingly, these activities are novel and unexpected in the *cis* isomers of Applicant's invention.

Instead of teaching one of skill in the art that the *cis* isomers have beneficial properties, the prior art guides the skilled person away from the compounds of the invention. For example, U.S. Patent 2,843,591 discloses that dihydrotetrabenazines and analogs thereof have various biological properties including sedative and blood pressure reducing activity.[21] Both of these properties would be considered to be undesirable side

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[19] *Id.* at page 18, lines 23-27 (emphasis added).
[20] Applicant's specification at page 49, Table 6, see entry (j).
[21] U.S. Patent 2,843,591, see col. 2, line 69.

effects in a drug intended for the treatment of movement disorders. Therefore, a skilled person looking for a drug capable of treating movement disorders would be dissuaded from investigating dihydrotetrabenazines.

Similarly, the Brossi article[22] discloses in the section headed "Resultate der Pharmakologischen Prüfung" that "*Some of the 2-hydroxy-hydrobenzo[a]quinolizines referred to display sedative and narcosis-potentiating effects.*" Brossi also discloses that *trans*-2-hydroxy-3-n-butyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]-quinolizine hydrochloride (a very close analog of dihydrotetrabenazine) has a marked protracted blood pressure-reducing effect on animals. In addition, the Brossi article contains further indications that dihydrotetrabenazine and its analogs are toxic. Thus, in the second full paragraph of the section headed '*Resultate der Pharmakologischen Prüfung*", the properties of esters of the dihydrotetrabenazines are discussed and it is disclosed that the esters are less toxic than the parent dihydrotetrabenazines.

Therefore, one of skill in the art would understand from the Brossi article that the dihydrotetrabenazines, while exhibiting milder side effects in some cases than the corresponding ketone compounds, nevertheless do exhibit undesirable side effects and are considered to have toxic properties. Moreover, the skilled artisan, having read U.S. Patent 2,843,591 would not be motivated to make further investigations into other isomers (e.g., *cis*) of dihydrotetrabenazines. Instead, one of skill in the art would be more likely to make chemical derivatives of dihydrotetrabenazines (e.g. further esters) in an attempt to find compounds having the desired activity but without the toxicity.

For these reasons it is clear that one of skill in the art would not be motivated to pursue synthesis and isolation of 3,11b *cis*-dihydrotetrabenazines.

Only with hindsight knowledge of these desirable properties, can the Examiner argue that it would have been obvious to select a particular *cis* isomer and undertake the arduous synthetic and separation procedures required to make the isomers of Applicants' claims. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008)(citing

[22] *Helv. Chim. Acta* at 119, 128 (1958); *see* Translation of Brossi article at page 5.

Graham v. John Deere Co., 383 U.S. 1, 36 (1966)). The application of hindsight is inappropriate where the prior art does not suggest that this enantiomer could reasonably be expected to manifest the properties and advantages that were found for particular isomers. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008). When the therapeutic properties of an enantiomer are unexpected that enantiomer is not obvious in light of the known racemate. *Id.* (citing *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263, 1269 (Fed. Cir. 2007)). Here, the *cis* isomers of the dihydrotetrabenazine do have unexpected properties, and no synthetic procedures were available to make these *cis* isomers relative to prior art compounds. Therefore, the subject matter of Applicants claims is nonobvious in view of the combination of Kilbourn and Williams.

Applicant respectfully requests withdrawal of this rejection of claims 35 and 42 under 35 U.S.C. 103(a).

Claim 36, 38, 39 and 49

Claims 36, 38, 39 and 49 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kilbourn in view of Reich et al. (U.S. Patent 6,462,069; hereinafter "Reich"). The Examiner alleges that it would be obvious to formulate compositions comprising the isomers in substantially pure form, and substantially free of the *trans* isomer, in view of Kilbourn's teachings on the C-2 α and β isomers of dihydrotetrabenazine and Reich's teachings that compounds most preferably are used in a form that is at least 99% of a single isomer (citing Reich at col.16, lines 7-8).

However, there was no method in the art for making Applicant's *cis* isomers because, to Applicant's knowledge, the *cis* isomers did not exist in any form, even in impure form. If the *cis* isomers were present in some undisclosed composition or location, Applicant submits that the *cis* isomers were present in only minute amounts. As described above, while the *trans* isomers have been known for 46 years, no one had made and/or isolated the *cis* isomers until Applicants did so. Kilbourn informs the skilled artisan that the only available isomers of dihydrotetrabenazine are the *trans*

dihydrotetrabenazine isomers, and that *extensive* NMR studies were performed to establish this fact.[23] Kilbourn also fails to provide any useful teachings about how to make Applicants' *cis* isomers, further contributing to a skilled artisan's understanding that only the *trans* isomers of dihydrotetrabenazine were available. Thus, one of skill in the art could not simply purify the *cis* isomers from the existing *trans* isomers, and would facing the daunting task of developing wholly new procedures for making alternate isomers without the benefit of knowing which isomer, if any, of the dihydrotetrabenazine compounds might have useful properties.

Nor does Kilbourn disclose or teach compounds that have negligible binding to dopamine receptors, that avoid the sedative side effects associated with tetrabenazine and/or that have antidepressant activity. Accordingly, Kilbourn fails to inspire the skilled artisan to look for Applicant's compounds, or any compounds with such properties.

Reich adds nothing to cure the deficiencies of the Kilbourn article. In fact, Reich discloses nothing whatsoever about tetrabenazine or dihydrotetrabenazine. Reich is limited to amino-pyrazole compounds that are unrelated to Applicant's compounds. Even if Reich does teach that isomers are preferably at least 99% pure, Reich provides no method or reason for making Applicant's compounds. Nor does Reich inform the skilled artisan on why or how to select one dihydrotetrabenazine isomer over another. The paltry and unrelated teachings of Reich serve only to confuse one of skill in the art and are so unrelated to the subject matter of Applicant's claims that they guide the skilled artisan away from seeking Applicant's isomers.

Nothing in Reich or Kilbourn would guide or motivate one of skill in the art to seek Applicant's isomers for the additional reason that this combination of references fails to disclose the unexpected and advantageous properties of Applicants' isomers. Nowhere does Kilbourn or Reich teach that the *cis* isomers have negligible binding of dopamine receptors. Nowhere does Kilbourn or Reich teach that the *cis* isomers avoid the dopaminergic side effects encountered with tetrabenazine. Nowhere does Kilbourn or Reich teach that the *cis* isomers avoid the sedative side effects associated with

[23] Kilbourn, page 249, right column; Figure 1.

tetrabenazine. Nowhere does Kilbourn or Reich teach that the *cis* isomers have antidepressant activity. Accordingly, each of these activities is novel and unexpected in the *cis* isomers of Applicant's invention.

Applicant respectfully requests withdrawal of this rejection of claims 36, 38, 39 and 49 under 35 U.S.C. 103(a).

Claims 47 and 48

Claims 47 and 48 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kilbourn in view of Berge et al. (J. Pharm. Sci. 66: 1-19 (1977); hereinafter "Berge"). The Examiner asserts that Berge teaches that the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form (citing Berge at page 1, column 1) and that methanesulfonic acid is a potentially useful salt form (citing Berge at page 5, Table III).

Claim 47 depends from claim 35 and recites that the 3,11b-*cis*-dihydrotetrabenazine is in the form of an acid addition salt.

Claim 48 depends from claim 47 and states that the acid addition salt of 3,11b-*cis*-dihydrotetrabenazine according is a methane sulphonate salt.

Applicant submits that the combination of Kilbourn and Berge not only fails to disclose *cis*-dihydrotetrabenazine salts but also teaches away from such salts.

As described above, Kilbourn teaches one of skill in the art that the configurations at the C-3 and C-11b positions are fixed in the *trans* position so that only the trans isomers of dihydrotetrabenazine were available.[24] Kilbourn made this conclusion after *extensive* NMR studies[25] not only of dihydrotetrabenazine, but also of tetrabenazine and related benzoisoquinolines.[26] Nor does Kilbourn teach any synthetic procedures or advantageous properties for dihydrotetrabenazine isomers that would guide one of skill in the art to make and use the *cis* isomer over the compounds disclosed in Kilbourn. For

[24] Kilbourn, page 249, right column; Figure 1..
[25] Kilbourn, page 249, right column.
[26] Id.

example, Kilbourn fails to describe the surprisingly beneficial properties of 3,11b-*cis*-dihydrotetrabenazine isomers. Thus, the finality of the conclusion expressed by Kilbourn that only the *trans* isomers exist would discourage one of skill in the art from seeking 3,11b-*cis*-dihydrotetrabenazine isomers, let alone their salts.

Berge does nothing to cure the defects of Kilbourn or guide anyone to make and use 3,11b-*cis*-dihydrotetrabenazine isomers salts. Instead, Berge is limited to general information on pharmaceutical salts. Nowhere does Berge mention dihydrotetrabenazine or tetrabenazine, or any isomer thereof. Nowhere does Berge disclose or teach anything whatsoever about salts of dihydrotetrabenazine or tetrabenazine.

Instead, Berge teaches away from the predictability of one salt versus another, as follows.[27]

> **Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.**

Therefore, Berge informs one of skill in the art that no one can predict which salt may be better than any other.

Berge lists many types of salts.[28] Rather than providing specific guidance about how and why one of skill in the art should select an acid addition salt of 3,11b-*cis*-dihydrotetrabenazine, or a methane sulphonate salt of 3,11b-*cis*-dihydrotetrabenazine, Berge informs such a skilled artisan that there is no reliable way to predict which salt will have the desired pharmacokinetic, solubility and formulation profiles.

Moreover, because the combination of Kilbourn and Berge do not provide specific teachings on which salts to use with 3,11b-*cis*-dihydrotetrabenazine isomers, one of skill in the art would be guided by Berge's general teachings that the hydrochloride

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[27] Berge, page 1, right column.
[28] See, e.g., Berge Tables I and II.

salt is the most commonly used salt.[29] Based on Berge's teachings, the skilled artisan may also select the chloride, or the acetate, or the iodide, or the maleate salt – all of which Berge teaches are more commonly employed than the methane sulphonate. However, even if one of skill in the art were to select one of the salt types listed by Berge, that skilled artisan would know from Berge's teachings that:

> The number of salt forms available to a chemist is large; a survey of patent literature show numerous new salts being synthesized annually. Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound. For example, a salt's hydrophobicity and high crystal lattice energy can affect dissolution rate and, hence, bioavailability.[30]

Accordingly, Berge teaches the skilled artisan that the chemical, physical and physiological properties of a pharmaceutical salt are wholly unpredictable. Hence, the skilled artisan would have no reason to select the methane sulphonate salt over any other salt. In view of this uncertainty, one of skill in the art would be motivated to select salts that others have used successfully such as the hydrochloride, the chloride, or the acetate, or the iodide, or the hydrobromide, or the pamoate, or the maleate – all of which Berge teaches are more commonly employed than the methane sulphonate.[31]

Thus, the combination of Kilbourn and Berge teaches away from selecting a particular acid addition salt (for example, a methane sulphonate salt) of 3,11b-*cis*-dihydrotetrabenazine.

The Examiner has failed to make a prima facie case of obviousness and Applicant respectfully requests withdrawal of this rejection of claims 47 and 48 under 35 U.S.C. 103(a).

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[29] Berge Table I.
[30] Berge, at page 2, left column.
[31] Berge Table I.

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 29th day of July, 2009.

John D. Gustav-Wrathall

Name

/John D. Gustav-Wrathall/

Signature